THE ETIOLOGY AND PREVENTION OF PELLAGRA

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The Etiology and Prevention of Pellagra.

Pellagra is a disease characterized by gastro-intestinal, digestive, nervous and mental disturbances, usually running a chronic course, with periodic exacerbations, but sometimes developing acutely and proceeding quickly to a fatal termination. In most text books of clinical medicine at the present time the disease is associated with the diseases of metabolism and states of mal-nutrition. Others, however, place it among the infectious diseases, admitting, however, that the cause of pellagra is still unknown.

History. The disease doubtless occurred in ancient times, but was not recognized as a definite entity until 1730 when Casal[1] studied it in the Asturias, observing that it occurs among the peasants who live chiefly on corn and rarely eat fresh meat. At this time it was known among the peasants as mal de la rosa (disease of the rose) the name by which he described it. It is certain that pellagra was by no means a new affection when it was many years later discovered by Frapolli in Italy. He also says the name was of popular origin and the appellation by which it was generally known among the people of the country districts among whom it occurred. The name no doubt is derived from the Italian words, pelle, skin, agra, rough. As the disease spread throughout the maize-eating provinces of Southern Europe it was called by a great variety of names,- pellagra, mal de la rosa, alpine scharg, Asturian leprosy, maidismus, etc.

We have no certain knowledge as to either the precise period when pellagra first made its appearance or in what part of the world it

Navarre began. It is thought by some that this affection existed in the new world at a period that far antedated the discovery by Spain. This view is particularly upheld by those who are advocates of the maize theory of the etiology of the disease. It is pointed out by such writers that the population, particularly of Mexico at the time of the conquest, subsisted largely or almost entirely on this cereal and if these theories are correct as to the cause of the disease, pellagra must have been quite common among the natives at the time. Evidence, however, as to whether the disease did really exist among them seems, however, entirely based on the maize-theory of causation.

As regards the development of pellagra in Europe, it is asserted that the disease made its appearance early in the eighteenth century, and as mentioned from the first observed by Casal in the province of Asturia in northwestern Spain. His studies were not published till thirty (7) a French physician stationed in Spain, had the manuscript, and on his return in 1755 published Casal's observations. Frapoccio (7) described the disease in Italy in 1771, followed in 1786-1794 by the four famous publications of Strambio (20) on the subject. In 1805-1808 Bunivo (7) by a series of inoculations in the Roman Prisons showed that in all probability pellagra is not an infectious disease. Frapoccio (7) wrote a monograph in 1807 in which he suggested the food-like relationship of maize resembling in pellagra, and followed by others who maintained that the use of this cereal as a food is alone responsible, due to the lack of proteins contained. The theory

that the disease is due to moulded maize was first
forwarded by Lavaracchi[7] in 1864. He confirmed his
views in 1870. In 1845 Billardini[7] wrote a
monograph on the relationship of fermented maize to
pellagra.

In 1836 pellagra was described in Lombardy
by Rabiles[2] who says that the disease appeared there as
early as 1818, and has subsequently been found in
all sections of that country, as well as other states
in Southeastern Europe. In 1894 the disease was noted
in certain of the Russian Provinces. Nibbi[8] in 1897
announced that pellagra exists in Mexico, espec-
ially in Yucatan. pellagra

In 1910 Lombroso[5] announced that he was
to ascribe the causation of maize, but that it
is a disease produced by a parasite transmitted by
goats (Simulcrum). These views were also indorsed
by the Thompson-McFadden Pellagra Commission[27]
which was formed to investigate the disease in
the United States. Sambon's investigations followed
the announcement of the prevalence of the disease
in the British West Indies.

The first cases of pellagra in the United
States were reported in 1864 by Gray[6] in New York
and by Lyon in Massachusetts. This, however,
is denied by Harris[17] of Atlanta who has recently
written a treatise on the disease. He claims to
have reported in 1902 the first undoubted
case of pellagra originating in the United
States. In 1906 attention was again called to
the matter by Searcy[18] of the Alabama Asylum
for Negroes situated at Mt. Vernon. Somewhat
later the subject was taken up by Babcock[19]
of Columbia, S.C., who has probably done
more than any one else to call the attention
of the medical profession of the United States

to this disease. It has gone over the records of the asylum at Columbia and has satisfied himself that pellagra goes back to the time of the institution in 1828.

As to geographical distribution pellagra has been reported from such widely separated places as Europe, Egypt, Asia Minor, Mexico, New Caledonia, and the United States. It has been recognized on the Isthmus of Panama, in British Guiana, Porto Rico, the Bahamas, Hawaii, the Philippine Islands, and from widely separated colonies in Africa. We must conclude that pellagra is obviously a disease of world-wide distribution, and although probably still unrecorded it is found in all countries inhabited by man.

Theories as to Causation of Pellagra:

It would be difficult to find any other disease which has given rise to so much speculation in regard to its cause. This question has been to a certain extent neglected in the past by serious investigators adequately trained in scientific methods to deal with the subject, while it has received much attention from the theorists who have added a great deal to its difficulties by their speculations. It is not the aim in this paper to discuss at length all the different theories and theorists that have been put forward as causes or explanations of pellagra, but to quote most of the time and space to representative ideas on the subject. It may be of interest, however, to say a few words on the most important of the various theories, taking them up, more or less in chronological order.

With but few exceptions the earlier writers made no attempt to assign any particular etiological factor

in pellagra, contributing stimulus as a rule with certain attention to those obvious debilitating influences with which the inhabitants of pellagrous districts are constantly brought in contact. As we know that most upon the objective symptoms of the disease is closely identified with conditions of this time, studies of pellagra are not without interest, dealing with those factors which are at the present time regarded as predisposing causes. Thus Castle[1], the discoverer of the disease, looks for the cause of the disease in the heavens, in the temperature and constitution of the air, and the diet of those so afflicted, and he opens the discussion of the subject with the observation that maize is the chief food of those suffering from this trouble, that in addition he mentions a number of vegetable substances, along with a small amount of milk, eggs, butter, and cheese. He noted that they seldom have meat. He was opposed to the view that the malady may come from atmospheric conditions, since all the moist and dreamstances would suffice. His report also states that the disease is simply sporadic, but finally adds it may be regarded as a disease from the heavens or heredity.

Prospero[7] in Italy also wrote on pellagra and considered insolation as the true and only cause. Others as follows in him also agreed with him as to the moist cause, but also suggested cereals, grains, and bad vegetables, as being strikingly factors, particularly calling attention to a suppose relationship to rancid butter and oils. He found that the malady was particularly common in hypothetics, while there at the same time suggested that it was most probably hereditary.

Strambio[20] who was perhaps the greatest of all pellagrologists recognized as possible factors the depression, dampness, smoky, rich in fatty foods, including fusel oils, and particularly maize, which he stated was often of poor quality. He emphasized the relationship between pellagra and dry localities, and noticed that prolonged and heavy rains were frequently followed by a development of the disease. He was also inclined to think that the disease is hereditary, but did not think it contagious nor of parasitic origin.

Fracanel[7] proposed the extraordinary theory that pellagra might be due to the light and cold in the Alps making the human stomach of the Lombardy plains. He was one of the first to urge strongly that there is a close relation between pellagra and maize, and stated that the disease is very common in the subalpine plains where the grain does not mature and that it is particularly frequent in those years when a dearth of wheat has compelled the use of maize soon as the season advances. Zanzago, in 1807, was really the first writer who definitely asserted that maize is the cause of pellagra. Following these writers came many theories as to whether the disease is due to immature maize, fungous growth in maize, insufficiency of maize as the principal article of diet, maize smut (Lombroso,[7] 1870); toxic products of maize (Selmi,[7] 1876-77); underdressed bread (Tuke,[7] 1869); autointoxication theory (Meissen,[12] 1887); mixed yeast and mouldy maize (Gherardi,[11] 1905); phytogamic substances in maize (Aschoff,[13] 1908); and the theory of insufficiency of so-called vitamins (Funk,[14] 1911).

In 1869 Lombroso[15] published a classical treatise on pellagra. He at all times maintained the causal relationship of bad maize to pellagra and wrote so

much on the subject that this view of the etiology of the disease is frequently called "Lombroso's theory." However, his only contribution of importance to this phase of the subject was his hypothesis that poisons are produced in maize by the growth of micro-organisms and that these products are the real agencies involved.

Predisposing Causes of Pellagra:

Most of those who have written on this subject in the past have agreed that any and all agencies that tend to lower the vitality and cause deterioration in the general health play an important part in the production of pellagra, meaning by the term these symptoms which periodically recur and which when taken together have been regarded as constituting an attack of the disease. As the symptoms often brought about are often of the gravest severity and frequently their life history and termination are matters of great importance.

It would appear beyond question that the sun's rays act most deleteriously upon pellagrins, not only roughening the skin lesions, but causing an outbreak of all the other symptoms. No doubt this is due to the action of the ultra-violet or chemical rays of the light. In addition it is to be noted that the heat of the rays of the sun simply overcomes the delicately balanced metabolism of those suffering from the disease in latent form and causes it to precipitate the attack.

It is worth reason that season exerts a great influence on the development of the various recognized symptoms or manifestations of the affection, these occurring towards the end of winter and spring and in the autumn. Dr. A. (16) Marie and Dr. Goodbody and Wheeler also record reports to Goodbody and Wheeler also record reports to the same effect to be the case. They made a study in their respective fields - more religious

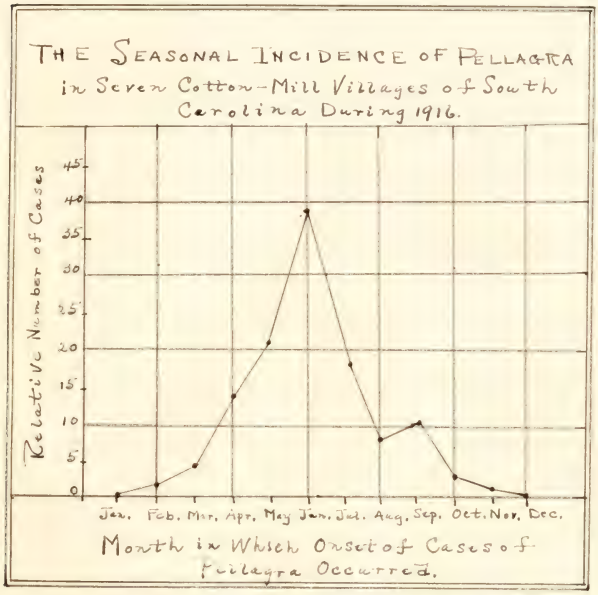
villages of the Piedmont district of South Carolina. Their results are summarized in the following table and graph:

Monthly incidence of pellagra during 1916 in Cedar-mill villages.

Month	Males			Females			Total		
	Number of Cases	Number of cases in 31-day month	Monthly % of Cases	Number of Cases	Number of cases in 31 day month	Monthly % of Cases	Number of Cases	Number of cases in 31 day month	Monthly % of Cases.
January	0	0	0	0	0	0	0	0	0
February	0	0	0	1	1.1	1.4	1	1.1	0.9
March	3	3	7.4	1	1.0	1.3	4	4.0	3.4
April	6	6.2	15.3	7	7.2	9.5	13	13.4	11.5
May	7	7.0	17.1	13	13.0	17.1	20	20.0	17.1
June	12	12.4	30.3	25	25.8	33.9	37	38.2	32.7
July	3	3.0	7.4	15	15.0	19.7	18	18.0	15.4
August	1	1.0	2.4	7	7.0	9.2	8	8.0	6.8
September	6	6.2	15.3	4	4.1	5.4	10	10.3	8.8
October	1	1.0	2.4	2	2.0	2.6	3	3.0	2.6
November	1	1.0	2.4	0	0	0	1	1.0	.9
December	0	0	0	0	0	0	0	0	0
Totals	40	40.8	100	75	76.2	100	115	117	100
Monthly average		3.4			6.4			9.8	

These results are presented in a graphic manner on the following page. As may be seen there was a sharp rise in incidence during April and May, reaching a well-defined peak in June. This was followed by an abrupt decline during July and August which halted during September, but was resumed quite sharply during October. The seasons of onset appeared to be confined almost entirely to the six months, April to September, inclusive, and the period of greatest incidence occurred with the four months, April to June inclusive. The monthly incidence of attacks among males and females appeared

to be similar, with the exception of a decrease rise for males in September. The number of cases is too small, however, to warrant attaching much significance to the irregularity.



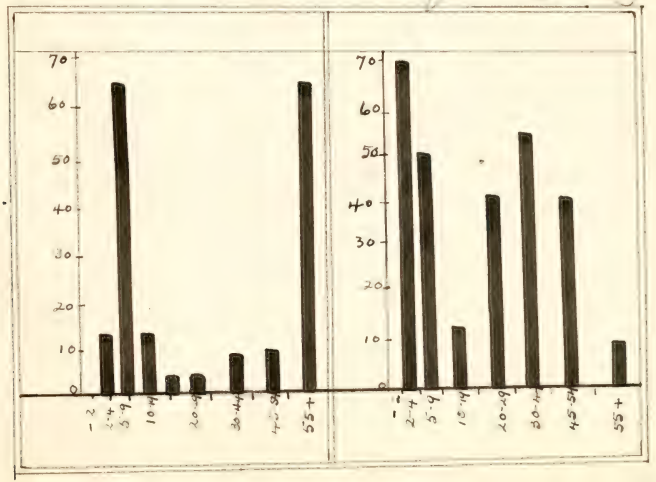
What is the causation of this periodicity in symptoms? The free discussion of this question must be deplored till we have a plan of the probable etiology of the disease. In explanation of the tendency referred to, miasmatic theories have been resorted. It is thought by some that the coming on of the symptoms in the late winter and spring is a consequence of the poor food and unhygienic condition surrounding the poorer classes during the winter; it is pointed out that the is longer continued to the house which is often poorly ventilated, that he has little variety in food, and that he suffers from a lack of the vegetables from

which he profits so abundantly during the summer. It is a well-known fact that the dietary habits of the people undergo considerable change with the seasons. For instance, in the general population, more meat is eaten in the winter than in the summer. It is quite possible then that during the winter the poor, who suffer chiefly from poverty, live mainly on flour, corn meal, canned beans, salt pork, molasses, etc.; that they are thus subject to a deficiency, which after a definite period of several months, produces lesions in the spring; and that when fresh vegetables and fruits appear in the market in the spring and summer the consumption of such food supplies the deficiency and the disease improves; it seems then that the following spring after the patient has been subject to the same deficiency, coincident with this is the exposure to the sun which returns occurs is probably of some importance in connection with this form of the subject since it has been clearly shown that this is one of the most potent factors in the precipitation of all pellagrous attacks.

In addition to the foregoing causes it is well known that there are many skin eruptions that have a marked tendency to develop in the spring, some of which conditions are probably of a similar nature. Thus (18) Duhring has shown that herpes zoster is much more rarely seen and is found most frequently in the spring. As a further example of this seasonal variation, the prodromal manifestations of urticaria pigmentosa, it being well known that in children the eruption produced by this plant often occurs about the same time of the year for a number of seasons.

A further factor in the predisposition to pellagra no doubt is "bad hygiene". The word is used in a broad sense, according to Harris[17] to denote anything that lowers the metabolism of the pellagrin ultimately become in some instances that an attack of the abdominal symptoms may be brought about by the slightest disturbance of the most trifling mishap, or some other debilitating influence of sufficiently significant character that it would pass unnoticed under ordinary circumstances. Among these influences that have been suggested by various writers are imperfectly cooked food, indiscriminate eating of fruit, abuse of alcohol, dark, ill-ventilated and humid habitations, filthiness, excessive fatigue, excessive worry, and other depressing influences of all kinds.

In a recent report Goldberger and Wheeler[16] have shown that diet and age both have an important place among the predisposing causes of pellagra. This is very well illustrated in the following diagram:



The data appear to indicate that the disease is rare in children at the age of 2 and under; that among both males and females up to 20 years the incidence is similar, being higher among children between 2 and ten years than in periods of the ages 10 to 19, inclusive; and that among adults 20-54 years old the incidence is many times higher in females than in males. What are the explanations of the statistics of the incidence of pellagra being higher among females in the United States? In a study of pellagra in the mortality experience of the Metropolitan Life Insurance Company, Dublin[19] also has shown that the rate for females is higher than for males both among the white and the colored. This Company has data covering a period of six years, from 1911 to 1916, during which time pellagra has greatly increased in its incidence. The operations of the Company cover a large part of the pellagrous area of the country. In the several million cases in the cities and towns of the South are included, white as well as colored persons, in fact every group of the population except the negro one is fairly represented. As mentioned above there is a marked difference between the rates for males and females. This is found at virtually every age period. The greatest difference is found among the colored at each age period the rate for females is a number of times higher than the rate for males. It would be interesting to learn why females in this country have such a high incidence of pellagra, since a number of other countries where pellagra has been prevalent, no such relation between the sexes has been observed. In Italy, for example, according to Dublin, the rate for 1913 was higher for males than for females. Rhumanian and Egyptian statistics according to the same writer, do not show

of female deaths from pellagra. The following table shows the mortality from pellagra classified by color, sex, and age periods, the death rates per hundred thousand, 1911-16, according to the experience of the Metropolitan Life Insurance Company. The record is based upon an experience of 2,310 deaths from the disease:

Mortality from Pellagra according to Color, Sex, and Age for 100,000 Population, 1911-1916.

Age period	Persons	White		Colored	
		Males	Females	Males	Females
All ages	4.3	1.6	3.9	6.4	20.7
1-4	.4	.2	.5	2.3	1.5
5-9	.3	-	.2	2.3	3.5
10-14	.6	.2	.5	2.7	3.4
15-19	.9	.3	.9	1.3	6.2
20-24	2.8	.3	2.5	2.3	19.8
25-34	5.5	1.4	4.8	4.6	24.5
35-44	8.9	2.9	8.4	8.8	31.1
45-54	9.2	4.1	8.1	15.3	30.9
55-64	13.0	10.9	10.1	19.2	39.2
65-74	11.9	10.3	8.8	21.7	41.1
75 & over	10.1	9.9	5.0	41.2	45.4

This table indicates clearly that pellagra has its lowest incidence as a cause of death in the ages of childhood; in fact the number of deaths among white children under 15 is negligible. Colored children show a larger number of cases. After 15 the rates increase regularly until the age period 55 to 64 is reached. From this point onward the rate faces slightly. It is significant, however, that each of the color and sex groups shows during the main period of life a high rate in-

cidence of pellagra as a cause of death for each advancing age period. Age is therefore of much importance in the predisposition to pellagra.

Dublin has also shown that race has a very important place as a predisposing factor in the causation of pellagra. This is also clearly brought out in the above table of death rates. The disease is much more prevalent among the colored. This is true at every age period and for both sexes. In fact the rate is four times as high for the colored males as for the white males, sexes combined, and more than five times as high for the colored females as for the white females. This condition is most probably the result of the different geographic distribution of the colored people, these who live in the great part reside in the southern states where pellagra is more common. It has been pointed out by Ivaldi that the Jews enjoy a relative immunity to the disease in Roumania. Still more recently similar observations have been made in the United States. It may be that the frequent efforts, running, or the menstrual losses accounts for the high incidence in women.

Harris[71] claims that dyspeptic disturbances play a very important part in the development of pellagra. Whether these conditions are the result of the latent disease or whether the dyspeptic condition occurs independently, he claims that an overwhelming proportion of pellagrins give a history of disturbances of this kind, usually for many years previous to the onset of clinical manifestation of the disease. Harris also has frequently observed, particularly in women, the

pronounced effect referred to mental anguish, a
very large proportion of these patients admitting
that their first active symptoms developed closely
following worry. The importance of such influences
were also recognized by Strambio.

It has long been believed that pellagra
is hereditary. This view has little support in Amer-
ica, but in certain European countries statistics
seem to show that some importance must be granted
to the assertion. Thus in Italy Calderini[7] showed
that of 1005 pellagrins - 449 men and 556 wo-
mitted to the city hospital in Milan from 1844 to
1846, inclusive, there were positive evidences of hered-
ity in 618 cases, and that such influences were
possible in 380 more. Of these patients 778 had
passed the age of 12 before being attacked. In
the light of modern ideas on the etiology of
pellagra and its relationship to mental and
economic influences one could not attach as
much to these statistics as formerly. Thus pellag-
ra shows an extraordinary frequency in hospitals
for the insane and functional psychoses. Conditions
of life, habits, or constitution of persons confined in
such a hospital may be such as to especially
favor the onset of pellagra, which, ede cause
or a deficiency, or intoxication. It
may be that the defective construction, whatever
it be which is responsible for the poor adaptabil-
ity and inelasticity of make-up, found in
many pellagrins, may have predisposed to the
development of the disease. Boudouard[21] found
such a relationship at the Alabama Insane
Hospital where 40 - one patients were attacked
with beri-beri. Among the of the patients who

subject of some psychic degeneration, form of mental disorder. It is apparent therefore that there is some close relation between such psychic states and a tendency to acquire such a disease as beriberi. If we accept the modern views, at least in part, concerning the cause of pellagra, this disease may possibly show heredity only in the being correlated with family peculiarities in respect to the taking of a correct or sufficient diet.

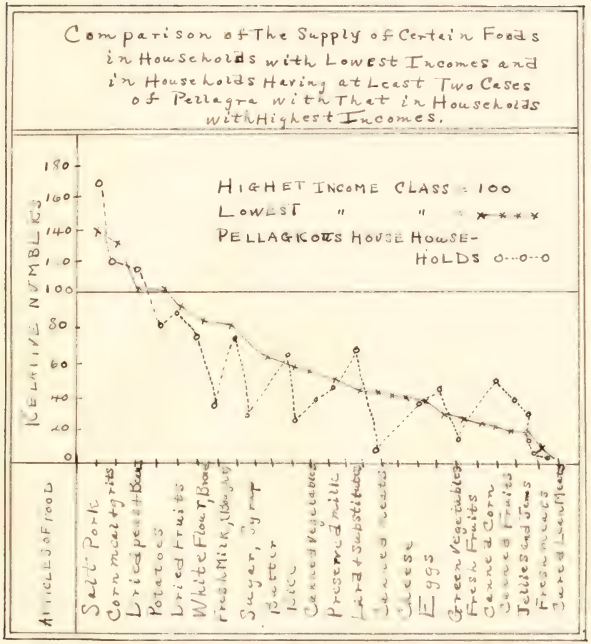
Goldberger, Wheeler, and Sydenstricker[23] have recently made a study of the relation of family income and other economic factors to pellagra incidence in seven cotton-mill villages of the textile districts of South Carolina. Pellagra incidence was determined by a systematic house to house canvass and search for cases, only active cases being considered. Information relating to household food supply, family income, etc., was secured. Family income was made the basis of classification. In general, the incidence of pellagra was found to vary inversely according to family income. As the income fell the incidence of the disease rose and showed an increasing tendency to affect members of the same family. As the income rose the incidence fell so that it was reduced almost to practical disappearance in the highest income classes, although the income here was comparatively quite low. The inverse correlation between pellagra incidence and family income was found to depend on the unfavorable effect of low income on the character of the diet, which was inadequate or

very low in certain articles of food, particularly milk and fresh meat. Upon a basis of half-month income per adult-male unit for each of the income classes and the corresponding pellagra rate per 1,000 persons, the Pearsonian coefficient of correlation was found to be -0.91 ± 0.05. The regression therefore indicates a high degree of correlation. For a family income of less than six dollars the adjusted case rate per 1,000 was 41.0, while for fourteen dollars and over, it was only 2.5. The following table taken from the report of Goldberger and Wheeler shows the number of definite cases of pellagra and rate per 1,000 among persons of different income classes:

Half month family income per adult male unit	Total			Males			Females		
	No. of persons	No. of cases	Rate per 1,000	No. of persons	No. of cases	Rate per 1,000	No. of persons	No. of cases	Rate per 1,000
Less than $6.00	1,312	56	42.7	650	20	30.8	662	36	54.4
$6.00 – $7.99	1,037	27	26.0	521	6	11.5	516	21	40.7
$8.00 – $9.99	784	10	12.8	376	4	10.7	408	6	14.7
$10.00 – $13.99	736	3	4.1	363	0	0.0	373	3	8.0
$14.00 + over	291	1	3.4	161	1	6.2	130	0	0.0
All incomes	4,160	97	23.3	2,071	31	14.9	2,089	66	31.6

The above rates seem to show that one of the most potent influences in the causation of pellagra are low family income and unfavorable conditions in respect to proper food supplies, for investigations, especially by Goldberger, Wheeler, and Sydenstricker have demonstrated the association of marked variations in diet with family income.

We shall now consider the most important of the theories regarding the specific factors in the etiology of pellagra.



(From Report of Secretary, Alabama, and Report (22)).

Theories of Causation.

Theory of Infection.

Suffice mention only will be made concerning the earlier views as to pellagra being caused by some infectious agent. Many of the earlier writers, especially Tuscus (7) in 1791, urged the idea that the disease was due to a contagium. It based his conception, however, on pure speculation. The same theory was put forward by Eidemann (7), Tonali, Peri (7) and others, to all refuted by Bonfigli (7), who made many efforts to inoculate the blood and secretions from the lesions of pellagrins into human beings. In 1881 Majocchi (23) the celebrated Italian bacteriologist announced that he had found in the meal from bad maize and also from the blood of pellagrins, an organism which he called the Bacterium maydis, and suggested that the grain might have an important bearing in connection with the causation of pellagra. Others found the organism in bad maize, but were unable to confirm Majocchi's observation of its occurrence in the blood. Further observations showed that the organism is identical with the potato bacillus and is found in the intestines of healthy men, and it was thus demonstrated that the Bacterium maydis is in no way specific so far as the cause of pellagra is concerned. In 1896 Lombroso described an organism which he described as Bacillus pellagrae, but nothing came of it.

There then followed a period during which many organisms were held to be more or less responsible as the etiologic factors in the production of the disease. Among these may be mentioned the mucus

[illegible] Cini[17] and Besta[17] conducted a series of experiments on the lower animals and convinced themselves that these organisms are highly pathogenic, not only when given by mouth but particularly when injected into the bodies of these animals. They claimed that the moulds were peculiarly virulent when introduced in connection with maize, believing that this substance exerts a marked influence upon skin tissues to produce poisons. Tasaki concluded that the ordinary preparations of this grain used as a food are not sterile and that of the organisms which still retain vitality after cooking is a streptothrix which is capable of producing a pronounced pellagra when injected into the rabbit.

The most persistent of those who assumed ascribe to a definite bacterium a causal relationship to pellagra is the Italian pathologist and bacteriologist Tizzoni,[24] who alone or in association with others, has made the claim that the disease is produced by an organism, known as the streptobacillus pellagrae, of which there are two types, A and B, the former considered as the fundamental form. Both are facultative anaerobes and Ramolight. Tizzoni and his coworkers claim to have succeeded in producing symptoms in various animals, including the monkey, which they have interpreted as affording clear evidence that pellagra has been transmitted to these animals. Other Italian workers deny that Tizzoni's streptobacillus is found in any large per cent. of cases of pellagra and that although certain symptoms and lesions may be produced by its injection into animals, it can not be recovered after many acute infections. Only one American writer, Mark,[25] has claimed to have isolated the streptothrix pellagrae from an actual case of the disease. On the other hand many investigators both in this country and in Europe have been unable

to confirm the claims of Siggeri. Sambon and Harris[32] have made communications from the bodies and blood of a large number of cases and also sought for this organism by means of cultures, but have hitherto failed to demonstrate its presence in a single instance. It may therefore be concluded that the organism has nothing whatever to do with the causation of pellagra.

McKee, Allison, and York[26] have made extensive and thorough investigations on the intestinal flora of pellagrins, but owing to the inherent difficulties involved in such a subject, came to no definite conclusions. They found that there is a marked change in the numerical relations of the different types normally found, as well as the presence of new species; there is often a marked diminution in the number of bacterial forms present. Protozoa are frequently found. It is very probable that these forms, however, are rather the result than the cause of the intestinal conditions found in pellagra. It is also highly probable that the food taken has a great influence on the types of organisms found in such cases. Attention should be called to the fact that there occurs in pellagra none of the specific foci or local areas of pathologic change that are in most cases so characteristic of infectious processes; on the other hand we find a general degenerative degeneration of all the tissues of the body, resembling very closely indeed the changes associated with senility.

In 1910 Long[27] advanced the theory that pellagra is due to intestinal amoebae, which he found in the stools of 50 persons out of 52 suffering from the disease. He suggests that the malady is the consequence of an infection to the intestinal mucosa by these organisms, resulting in an inflammatory process extending throughout the alimentary tract;

there is thus a consequent interference in the absorptive powers of the intestine and a decrease in the normal ferments produced by the various glandular cells of the tract. Later, owing to the long continued inflammation in the intestines, the pancreas and liver undergo certain changes which interfere with the quantity and quality of the digestive juices, with a reduction in the digestion and poor nutrition. The theory seems to be important from a nutritional standpoint. It is due to this reason that persons suffering with intestinal disturbances of all kinds, such as are common in this area, frequently become infected with these flagellates; indeed these organisms are common in the stools of normal individuals, especially following a famine. Recent investigations by Dobell[28] and other well known protozoölogists have shown that not only may Entamoeba coli be found commonly in the healthy intestinal canal, but also Entamoeba histolytica, Endolimax nana, and two other less known forms recently described. Their presence is therefore not of sufficient importance to cause the grave symptoms of pellagra in any case. Briefly the pathological changes to be characteristic of amoebic dysentery are entirely different from those found in pellagra where the latter is present. Again cases of long standing amoebic dysentery are in no sense [illegible] of pellagra.

Probably the most important evidence put forward in recent times in support of the theory that some infectious agent is the chief etiological factor in pellagra is that of Sambon[4,5] in 1910, and later endorsed more or less without reserve by the Thompson-McFadden Pellagra Commission[24] as well as by Jobling and Peterson[34] in their work on the sanitary aspects of the pellagra problem. Sambon began his investigations concerning the etiology of pellagra in 1900 at the request of the Italian Royal

on in Italy in regard to the mosquito transmission of malaria. In 1905 he published a memoir that pellagra was an insect borne disease, the causative agent, from analogy to malaria, probably being some minute protozoal organism. He argued that the disease, like malaria, and certain other insect-borne diseases had a zonal-wise distribution; that its main theory of its etiology had already been announced but its critical investigation; and finally that, if clinically and epidemiologically examined the disease exhibited all the features of an insect-borne infectious disease. During his studies in Italy Lombroso aimed to have gathered sufficient evidence to warrant his conclusions. He found that the disease was endemic if existed the same glandular distribution, its stations or endemic foci being irregularly scattered, and always confined to well-defined rural areas intersected by swiftly running streams; that in certain provinces both the areas of endemicity and immunity had kept their respective locations for at least a century. He noticed that within its endemic areas, the disease had affected at one time or another practically the entire population, being like malaria, especially common among the very young children. Lombroso also observed that pellagrous immigrants did not communicate their contracted disease to the inhabitants of non-pellagrous localities, notwithstanding the most intimate association; but in certain cases a previously immune locality may become an endemic center of the disease if there is immigration of pellagrins. He mentions the apparent fact that robust healthy people migrating to a pellagrous community may contract the disease within their first year of residence. Thus by a

process of infection, Sambon concluded that the disease must be due to an infective agent carried most probably by some insect. He incriminated certain flood-plain flies, viz. the family Simuliidae or Chironomidae or both. The insects frequently spoken of as sand-flies are found in the genus of the world. The females are very blood-thirsty but the males appear to be incapable of a diet of blood. They often occur in swarms, and attack not only man, but cattle, horses and poultry, and in some districts are more annoying than mosquitoes. One species, Simulium bivittatum has been known to kill cattle in the Marquesas Islands. In America the Simuliidae are very common and annoying, one species is supposed to be the carrier of Chicken cholera, at least has caused the death of thousands of chickens and turkeys in Texas and Louisiana. Sambon found them invariably present in the pellagrous areas he visited in Italy.

In his report on pellagra in the United States Sambon[5] arrives at practically the same conclusions which he formerly announced. He found the disease to be present in all the areas and collected much data in support of his theory, as well as proof against the common view at the time that pellagra is related in some way to the consumption of diseased maize, bringing forward two decisive facts against the maize theory. The first of these is the occurrence of pellagra in persons who have never eaten maize, and the second the absence of the disease amongst maize-eating populations living in close proximity to or in the midst of pellagrous areas. In a country where maize is widely cultivated and used as an article of food it may be difficult of course to prove the entire exemption of maize meal from the diet of the natives, especially within the latter limits of tropical or rural districts where its cheapness is a strong

fact in a country in which maize is not grown nor eaten there can be no difference of opinion. Lombroso, of course at this time did not know the benefits of the system in its attention of Goldberger in regard to the exclusion of maize as an etiologic factor in the causation of pellagra in the United States. He stated, however, that the occurrence of pellagra was common in the British Isles where little or none of this grain is eaten. He also collected much data while in the West Indies going to show that pellagra had existed there as well as in other countries for over a century, although recognition of the disease was relatively recent.

As evidence against the theory of insect transmission are the following considerations. Most authorities do not agree that pellagra is a disease of damp localities, occurring along the edges of streams where midges are most prevalent. It is true that the disease has occasionally existed in damp localities, as was the case in Spain where the disease was first discovered. However, it is maintained by many that the disease is far more common in dry than in wet localities. Strambio[20] mentions that the disease is far more common in dry sandy countries. Dr Frothee Marchant[7] has particularly advocated the view that dryness of the atmosphere is closely associated with production of the disease. In a recent investigation of the prevalence of pellagra in Nancy County, North Carolina, Wheeler[31] has found many cases at a high dry elevation of 3,000 feet or more. Harris[7] has also studied the question for Georgia and arrives at the same conclusions. This author visited a great many pellagrins in their homes and was never impressed with any connection between the presence of streams and frequency of the affection. It is desirable to know whether pellagra occurs in districts

where the *Anopheles* is entirely absent and that there are other places where this mosquito is very common without the existence of the disease. Bassi has recently shown that in the province of Lombardy there is no species of gnat which habitually attacks man, with a habitat restricted to the damp localities that gnats exist in abundance where pellagra is absent, and that in more than 500 persons not pellagrous, who were occasionally bitten by these insects, there was not the least indication that the disease had been transmitted to them. Besides fleas, lice, and bedbugs must be excluded because of the peculiar age and mode of distribution of the disease in different places and because of the relative immunity of farm and city people. Mosquitoes are excluded on account of their domestic habits, and because pellagra and malaria, though overlapping in places, show a decidedly inverse distribution.

We must conclude that there is little foundation for Sambon's theory by asserting that pellagra is most common in those places where mosquitoes most frequently occur. Maj has made a careful study of the blood in the disease, but has failed to find any characteristic change, nor did he succeed in finding any parasite which could be held responsible. It should also be noted that not only has no parasite been found in the tissues of pellagrins, but that no one has been able to reproduce the disease in the human body by inoculation, and that similar experiments on monkeys and other animals have likewise failed. In the beginning of their classic investigations on the cause and prevention of pellagra, Goldberger[32], Francis[32], Lavinder[32], and others made a comprehensive series of inoculations into monkeys to which others they were dealing with an infection. Blood, every kind of tissue, secretion, and excretion from

a considerable number of gross and fatal cases was obtained and inoculated in many considerable ways into over a hundred rhesus monkeys the results were entirely negative. Francis also made a culture study of the blood, excretions, and excretions of pellagrins by anaerobic methods which were also negative. In another experiment Goldberger and fifteen of his associates tried in every conceivable way to inject themselves with material from the lesions of pellagra, and with excreta from pellagrins, but without success.

In a paper published in the Public Health Reports in June 1914, Goldberger[32] called attention to certain observations which appear inexplicable on any theory of communicability of pellagra. These observations show that although in many asylums many cases of pellagra develop in inmates even after 10, 15, or 20 years' residence, thereby indicating that the cause of the disease exists and is operative in such asylums, yet at none has any of the employees contracted the disease, though living under identical environmental conditions as the inmates, and in many cases in most intimate association with them. Niles[32] also made a careful study of the records of the Georgia State Sanitorium. These showed that of 996 patients admitted in 1910 — excluding those that died, were discharged during the first year, or had pellagra on admission or within a year of admission there remained at the institution after one year 418, and of this number 32, or 7.65 % developed pellagra. There were 293 employees at the Sanitarium who were in more or less intimate association with pellagrins and lived in substantially the same or identical

inasmuch as the asylum inmates for at least one year. Pellagra developed in none of these persons. If the disease had developed among these employees at the same rate as among the inmates, then 22 of them should have contracted the disease. Another fact of great significance in the observations made at this time was that practically all were in children between the ages of 6 and 12 years, of whom over 52 per cent. were afflicted at the orphanage at Jackson. This seemed from its point to some other factor than an infection, for adults in general show a much higher case rate than children. None of the employees at this institution developed the disease, at the same institution in the group of 25 children under 6 years of age there were 2 cases and in the group of 66 children over 12 years of age there was but one case. Inasmuch as all lived under identical environmental conditions, the remarkable exemption of the group of younger and that of older children is no more comprehensible on the basis of an infection than is the absolute immunity of the asylum employees.

Lomz[33] has made a careful study of the spinal fluid in 106 cases of pellagra, practically every clinical type being represented. Summarizing the results of the investigation, he found that a lymphocytosis of the cerebrospinal fluid does not occur in pellagra, at least in uncomplicated cases; that a genuine xanthochromia in the spinal fluid is only occasionally observed, and that Lomz's colloidal gold chloride test is uniformly negative, while the Wassermann is negative with a few exceptions. Such spinal fluid findings seemed to him inconsistent with the conception that pellagra is an infectious disease of the central nervous system.

In a report concerning the epidemic of pellagra based upon a complete survey of the city of Nashville, Tennessee, Goldberger and Waring (34) have made the observation that there is a close relationship between the sanitary conditions of the different parts of Nashville and the incidence of pellagra, and that this tends to support the view that the disease is associated with poor sewage disposal. They point out that the poorly nourished individual is predisposed to contract many diseases which poor sanitation would oppose them. The sanitary conditions in those districts where pellagra is common are of the worst sort, in many instances there being nothing at all in the way of excreta disposal. Flies are a great nuisance, and during the summer the unprotected excreta is covered with them. Screening was usually absent from those houses where the disease was found. Of the total white population of the city, 60% live in sewered houses, the balance having only the surface privy. For the colored population, the proportions are reversed. Of the white cases of pellagra, only 16% originated in houses with sewer connections, and of these, most often they were in houses provided with the so-called alley sewer, a water privy in an outhouse at the rear of the domicile, most frequently in an unsanitary condition. For the colored the same was true except that the water privies were practically all of the alley sewer type.

In all the recent investigations concerning the etiology and prevention, as well as treatment of pellagra, the character and amount of the various foodstuffs consumed by pellagrins has received the greatest amount of attention. It

should be pointed out, as mentioned before in the discussion of the predisposing factors in the case of pellagra, that in the United States, especially the diarrheal tracts to a marked predominance. Goldberger has emphasized this fact, and says that most new cases develop in the spring or at the end of winter. Jobling and Peterson[34] in their survey of pellagra in Charleston found that nearly all cases had their onset in the spring and early summer. Many of the sufferers recover from their attacks of the disease during the late summer and fall, only to suffer a relapse during the following spring. Goldberger and his associates maintain that this is very characteristic of a dietary "deficiency" disease, such for example in the cases of beriberi. The diet of many of the poorer people of the South, during the winter, consists of corn bread, pork, and molasses, at least this is the principal diet. As such a diet is considered inadequate, owing to the deficiency of so-called protective elements or substances, the seasonal occurrence at the end of winter or spring is easily accounted for, for nearly all new cases develop after three months or more of confinement to such a food supply.

It should be mentioned that Jobling and Peterson[34] point out that from their observations, the physicians, and the class of people from which the new cases do up, consume relatively much carbohydrate and little protein, since they make liberal use of corn bread, corn grits, potatoes, biscuits made from bolted flour,

to other sick neighbors. Some give the history of having recently eaten eggs, butter, milk, milk and meat. They further emphasize that in the spring, summer, and autumn months a great deal of green stuff in the form of turnip tops, wild mustard, green peas and green onions are eaten. The cattle are eaten raw, the others cooked. During the summer, apples and peaches, as well as other fruits are cheap, and are liberally eaten.

Owing, however, to the enormous increase in the number of new cases of pellagra in Nashville and other cities of the South Jopin and Peterson (34) do not believe this high rate of incidence can be accounted for on the basis of food supplies. In the period from 1908-1914 the disease increased rapidly in Nashville, while during 1915 to 1917 the number of new cases was smaller and the mortality less despite the fact that the recognition of cases reported as pellagra had become more certain. There is thus a curve of increase and decrease in the pellagra mortality. Jopin maintains that dietary diseases do not show such a curve unless there is a corresponding improvement in diet; that there is no reason to believe that the great mass of the people had consciously altered their diet during the years of low mortality in Nashville. There was no profound economic change bringing with an era of prosperity, especially in regard to the industrial class which make up the pellagrous districts in the city. Food prices remained fairly constant during the entire period under consideration.

Thus in considering the relation of diet to pellagra Goldberger, Wheeler, Tolkin and Peterson, standing out as contradictory. They mention on the one hand that a definite number of cases develop in individuals partaking of a diet as varied and as wholesome as any advocate of the deficiency disease theory would demand, and also cases coming to their attention of pellagra developing in breast-fed infants of non-pellagrous mothers. On the other hand at least half of the cases developed in persons living on a ration low in protein, high in carbohydrates, and monotonous in character. They admit too that the pellagrous condition is favorably influenced by a change in diet, but that the experiments of Goldberger and his associates which claim to have produced pellagra in convicts are open to serious criticism, because the experiment was carried on in a pellagrous community.

Tolkin and Peterson (34) also made observations on the growth of pellagrous children, but were not led to suspect any marked metabolic derangement as a causative factor. The young children examined were found to be normal in height and weight, whereas the older ones many of whom had shown pellagrous symptoms for years were under height and below weight, but to an extent apparently not exceeding that which obtains for children in the poorer districts. They consider that in these cases the disease process caused retardation, rather than that the disease resulted from a factor associated with the retardation.

As far as the epidemiology of pellagra

is concerned, the work of Jobling and Peterson seems to show that "there are evidences of the disease being in some way conveyed from one patient to another; that it is a disease of poor and overcrowded city areas, a family disease or almost as frequently a disease "of the house next door." They do not consider it a family disease in the sense that the members live in the same house and eat the same food, but most frequently relations not living under the same conditions, but frequently associating, have one after the other succumbed to the disease. They found that there was a definite history of contact in from 85 to 90 % of the cases. The fact that cases developed in homes adjoining pellagrous is also emphasized in the report of the Thompson-McFadden Pellagra Commission. Such conditions would of course lead to great chances for contact. It was found that a colony of negroes degraded and surrounded by pellagrous whites, had a much higher incidence of the disease than other negroes not so situated although living under identical economic conditions.

The conclusions of Jobling and Peterson and the Thompson-McFadden Commission, however, may perhaps be explained as not at all contradictory to the newer ideas on diseases due to faulty nutrition. Goldberger[41] and his associates have definitely eliminated the spoiled meat theory in respect to the causation of pellagra, and although the experiments of McCollum[35] and his co-workers, using the biological method, have changed to a considerable extent the older ideas

of Funk in regard to "vitamins", still the fundamental ideas on the relationships of pellagra to a faulty diet remain.

The Deficiency Hypothesis:

It may be stated that the question as to whether pellagra is an infection or a deficiency disease, or combination of both is still open. Recent studies in beri-beri, scurvy, and rickets have thrown much light on the conception of what constitutes a deficiency disease. Briefly stated this conception is that there are certain hitherto unknown and unidentified chemical substances now as well as formerly, more or less loosely designated as "vitamins" that are present in small but varying amounts in different foodstuffs which are absolutely essential to normal metabolism. The list of these substances has been much reduced by recent investigations, however. Mc Collum and Davis through their studies with purified foodstuffs have pointed out that it is highly probable that there are essential in the diet but two substances of unknown chemical nature, and have shown that one of these is associated with certain fats, while the other is never found with the isolated fats of either animal or vegetable origin. (38) Stiles suggested that they provisionally be called "fat-soluble A" and "water-soluble B", because by their characteristic solubility in fats and in water respectively. They consider all such names as "vitamines", "accessory foodstuffs", "food hormones", etc., as misnomers, because they may lead to misconceptions of their real nature and importance in the animal economy of growth, maintenance, and metabolism.

Funk[36] in 1911 took up the study of the disease beri-beri. It had been observed that the symptoms could be produced experimentally in birds by feeding them exclusively upon polished rice for two to four weeks, while they remain for much longer periods in a state of health when fed only the unpolished grain. It had also been observed that an extract of rice polishings could effect a cure of polyneuritic birds, but the curative substance was not isolated. The term "vitamin" food stuff was used by Hopkins[37] who discovered that minute additions of milk to purified food mixtures composed of purified protein, carbohydrate, fats, and inorganic salts rendered them capable of inducing growth. McCollum[43] and others have shown by experimental feeding of rats and other animals that "seed mixtures, no matter how complex, or from what seeds they are derived, will never induce optimum nutrition; that seeds with tubers, or, seeds with tubers, roots and meat (muscle) will in all cases fail to even approximate the optimum nutrition of an animal during growth; that the only successful combinations of natural foods or milled products for the nutrition of an animal are (a) Combinations of seeds, or other milled products, tubers and roots, with dairy or collective, taken with sufficient amounts of the leaves of plants; (b) Combinations of such foodstuffs taken along with sufficient amount of milk to make good their nutritional deficiencies."

There are then two classes or groups of foodstuffs, - the "protective foods", which include milk, eggs, and the leafy vegetables; in the second group

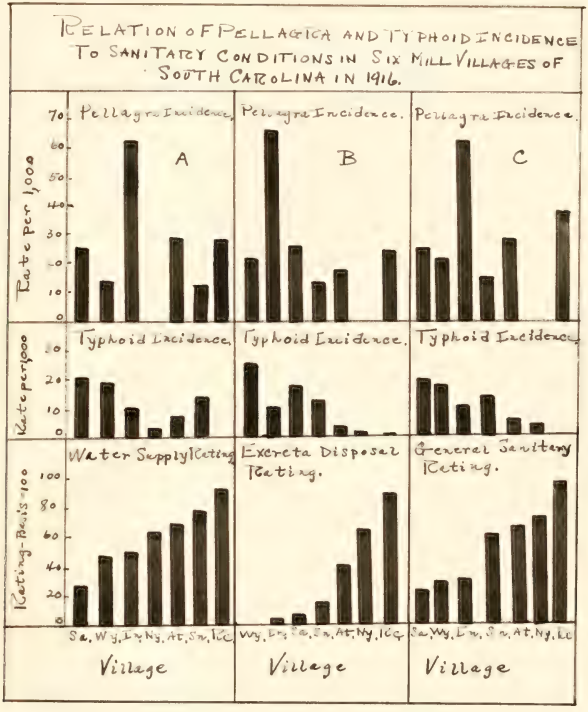
of natural foodstuffs are all seeds and seed products, tubers, fruits, and meat which is made up of muscle fibre.

As already pointed out Goldberger and his associates maintain that pellagra belongs to the group of deficiency diseases, while at the same time he has eliminated corn, particularly moldy corn, as a factor in the production of the disease. He has demonstrated that the diet when properly constituted, causes the disappearance of pellagra and prevents its recurrence. He has shown that when liberal amounts of milk and eggs and meat are introduced into the diet of institutions, such as insane asylums and orphanages in which the disease was previously common they become free from it, even though new cases are admitted constantly and allowed to associate intimately with the rest. An interesting experiment which was to be the crucial test of the whole matter of pellagra and diet was carried out by Goldberger (39) at the Mississippi State Penitentiary farm. A volunteer squad of twelve convicts, apparently perfectly free from the disease at the time of the beginning of the experiment, submitted themselves on the assurance of a pardon later. They were isolated from all others who had any symptoms of the disease so as to eliminate the possibility of communicability. They were strictly segregated and kept under guard day and night. The entire population of the "camp" of about 80 men were kept under close observation as controls. The volunteers were fed on a diet consisting of dishes prepared from degerminated corn meal, bolted wheat flour, rice, starch, sugar,

pork fat, tea etc. with sweet potatoes, cabbage, collards, turnip greens, and coffee. Of the [illegible] volunteers at the end of six and a half months, not less than six had developed symptoms, including a "typical" dermatitis, justifying a diagnosis at least of incipient pellagra. None of the controls produced evidence of even a suspicion of pellagra. The conclusion was drawn therefrom that the disease had been caused as the result of the restricted diet on which they subsisted. As already mentioned before, these experiments have been criticized on two grounds. Goldberger and Peterson who are upholders of the infectious nature of the disease point out that the experiment was carried out in a pellagrous community where the possibility of sanitary conditions playing an important role. McNeal (24) goes so far as actually to deny that the symptoms produced were incipient pellagra at all, as an insufficient number of experts took part in the diagnosis of the disease.

In a recent publication Goldberger and Wheeler (31b) have brought forward some very good evidence in support of their view that sanitation is not an important factor in pellagra incidence, which strengthens more than ever their former experiments and observations in regard to the role of diet. A sanitary survey and rating was made in eleven cotton mill villages of the South. The typhoid fever incidence and disposal of excreta were taken as indices of sanitary conditions. No correlation was found between the character of the water supply, method of sewage disposal, or typhoid rate, and the incidence of pellagra. Villages with the lowest ratings and highest ratings were found to differ little in respect to the incidence of the disease. Goldberger

and Wheeler conclude from these findings that "the disease is not an intestinal infection transmitted in much the same way as typhoid fever."



As seen from an examination of the above diagram taken from the report of Goldberger and Wheeler there is a definite correlation between the various sanitary conditions and the incidence of typhoid fever in the various villages. This, however, is not true in the case of pellagra for there is not only a great deal of irregularity in the incidence in the various villages, but in general no higher incidence in those places where the sanitary conditions are poor.

Analogies Existing Between Pellagra, Beri-beri, and Scurvy.

In making an inquiry into the relationship of pellagra and an inadequate diet it may be well to see if there are any analogies between the disease in question and other well known deficiency diseases. It is definitely known that these diseases are due to a lack or scanty supply of certain protective foods, and that such an insufficiency leads to the development of certain clinical and pathological pictures. Scurvy is characterized in one way by bleeding gums. In pellagra, according to Roberts, "during the outbreak the gums are inflamed in common with the rest of the oral mucosa. They are tender, spongy, and easy to bleed, as in scurvy." The gastro-intestinal lesions in pellagra and scurvy are analogous, both being usually characterized by diarrhoea, enteritis, colitis, and proctitis.

Similar nervous symptoms are found in pellagra (401) and scurvy. In general, according to Fraser, they consist of retardation of the mental processes and a general failing of depression which may go on to melancholia or other psychoses. The early symptoms, however, are usually much milder in scurvy.

The other similarities between pellagra and scurvy, apply almost equally well to beri-beri. Changes in the cord are found to be very similar in beri-beri and pellagra, consisting of a secondary vascular and fibre degeneration.

Such analogies of course do not prove that pellagra is a deficiency disease, but they at least are very suggestive. Analogies in other ways also exist. All are diseases of poverty or necessity. The distribution is chiefly among the poorer classes. Like beri-beri, pellagra shows an extraordinary frequency in prisons

and similar institutions where a large number of people live under comparatively good sanitary conditions but where the diet is often one-sided and monotonous in character. At the same time, as shown by Goldberger and others, it is very rare for doctors, nurses, or attendants living in close proximity and in close personal contact with these cases, but on a more varied dietary, to acquire pellagra. Harder agrees with the conclusions of Goldberger, that it is very difficult to account for the peculiar distribution of pellagra in these institutions on the basis of an infection. It is therefore hard to reconcile the observations of Jobling and Peterson and the Thompson-McFadden Commission with these results, found in certain of these institutions, especially the asylums, the disease might well be due to faulty or one-sided diet as well as peculiarities in habits of living, which has actually been observed.

It often happens that patients with pellagra sometimes become worse and die in spite of the fact that they are receiving an "excellent" diet. This point has been emphasized especially by those in favor of the infectious theory of the disease. This diet, however, may not have been rich in the necessary protective substances, or the patient may not have been able to assimilate them. These peculiarities, may probably be ascribed to personal conditions, and to the particular pathologic changes that have occurred which may be irreparable and lead to death.

As mentioned before, the seasonal incidence of pellagra points strongly toward the dietary hypothesis. The peculiar tendency to recurrence during the late spring, according to Goldberger, Wheeler and others, cannot be ignored so well on the infe

of the infection theory, done as no known infection acts in this manner. Beri-beri acts in precisely this way. The dietary habits of the people vary considerable Change with the seasons. In general more meat is eaten during the winter, than during the summer, but Goldberger and his associates have found that during the winter, the poor who are the chief sufferers from pellagra, live mainly on a diet of flour, cornmeal, molasses, canned tomatoes, salt pork, etc., which according to McCollum can not be classed as "protective foods." The diet is totally lacking in milk, eggs, and the leafy vegetables. These foods are protective in that they are so constituted with respect to their inorganic content, content of fat-soluble A, and the quality of their proteins that they correct in great measure when used in sufficient amounts the faults of the remainder of the food mixture (McCollum). Now pellagrins are subject to a deficiency, which after a depletion period of several months, produces lesions in the spring; and when fresh vegetables and fruits appear in the market in the spring and summer, the consumption of such food may supply the deficiency to a great extent at least, and the disease improves.

~~Is Pellagra an Infectious Disease, a Deficiency Disease, or a Combination of Both?~~

We have already indicated that pellagra is analogous in many respects to the well-known deficiency diseases, scurvy and beri-beri. Before proceeding to a fuller discussion of the relation of diet to pellagra, it may be well to consider some of the criticisms that have been offered by those who do not think the disease primarily at least due to some

infectious agent.

It has been noted by many that there is a definite tendency for a self-limitation of pellagrous attacks in the absence of specific therapy, and during the continuance of presumably the same defective diet that produced the disease. In some manner the clinical symptoms have disappeared, and it would appear to some to have a suggestive resemblance to an infectious disease. It may be answered, however, by origin that the substances which act as protective agents in various foods are still little understood chemically and it can hardly be said that the patient who receives has not received some nourishment that would cause a change in his condition.

As mentioned already, Jobling and Peterson have maintained that contact or close association with cases of pellagra has been noted in 90 % of the cases. This again seems to argue in favor of the infectious nature of the disease. On the other hand it is possible that this has little significance as half of the cases have occurred in members of the same family all taking more or less the same diet and living under similar economic conditions. Goldberger has shown that there is a close relationship between such factors and the incidence of the disease. It must also be remembered that pellagrins are not quarantined, and the general public is exposed to them in many ways, so that practically every one has come in contact with them.

In the report of the Thompson-McFadden Commission[29] we find: "The conception that pellagra is an infectious disease in some way transmissible to persons exposed seems to us to be strongly supported by field observations. The higher incidence of pellagra in the more populous districts and the indications of its occurrence in definite foci are in accord with

this idea." Such evidence, however, is not borne out by the statistics concerning the incidence in the cotton mill villages of the South. In Spartanburg, S.C., Goldberger and Wheeler[40] have found that the mill villages which are continuous with and a part of the city, present a rate of 142 per 10,000, whereas the remainder of the population living under approximately the same condition of congestion, gives an incidence of 29 per 10,000. This does not support the assertion that density of population alone has any relation to the spread of pellagra. It may well be, however, that the higher incidence of pellagra in the mill villages is accounted for by assuming that the population of this group are poorer economically and live on a poorer class of food.

Important evidence collected by Jobling and Peterson[34] and the Thompson-McFadden Commission[39] toward the infectious origin of pellagra is the study of the domicile of the cases. It is pointed out that the disease is much more common in those who live in the same house or an adjoining house to pellagrins. It may be, however, asserted that this evidence is as much in keeping with the dietary theory, for those who live in the same house with pellagrins are usually members of the same family and of course partake of the same food. Those who become pellagrous in adjoining houses are commonly people of similar economic standing and as a rule would eat the same kind of food. The well-to-do would be segregated as well in other sections. The same criticisms are offered by Wheeler[40] to explain the reason for a higher incidence of pellagra in these districts

having a primitive system of disposal of excreta. Thus in Nashville, as already mentioned, Goldberger and Peterson found the disease more commonly in those sections of the city having privies than in the sections provided with a sewer system. The poor people, however, are found in the unsewered sections, and here again the economic factor enters in the relation to proper diet. But the Commission is inclined to think that food is not an important factor, because they have been unable to implicate any special food or class of foods as the causative factor. Thus it is known that beri-beri is caused by eating polished rice, but no one definite food, except maize, has been implicated as the cause of pellagra. The Commission has shown that in this country at least the incidence of the disease is relatively higher among those eating corn meal rarely or never. Thus, of those using corn meal daily, 3.13 per cent. were pellagrins; of those using it habitually 4.3 per cent. were pellagrins; and of those using it rarely or never 6.02 per cent. had the disease. Obviously then corn as a causative factor must be dismissed from further consideration.

Again it has been objected, that if pellagra is a depriving disease, fresh meat, milk, and eggs, and the leafy vegetables ought to cure the disease. The commission found, however, that of the eighty-two persons in families using fresh meat daily 4.88 per cent. were pellagrins; of the 2,591 individuals in families using this food habitually, 3.74 per cent. were victims of pellagra; while of the 263 persons never using fresh meat 1.52 per cent. had the disease. Similar proportions

were found in regard to the use of eggs. The Commission is inclined to believe from the data that the disease is not caused by a dietary deficiency. Neal[40], Goldberger[41], and others have concluded, however, that the Commission did not consider in sufficient detail the quantities of the various foods used, for it is just as important to know the relative quantities of the different foods consumed over a definite period of time.

In general it may be said that the great bulk of the food of the poorer pellagrins consists of wheat flour, corn meal, potatoes, salt pork, and boiled vegetables, and that during the winter these latter are scarce, consisting chiefly of beans and cabbage. In some instances a considerable amount of canned goods are used, but most of them do not use these to any extent. Often cases of pellagra among the well-to-do may be found associated with an inadequate diet. Two such cases taken from the first report of the Thompson-McFadden Commission may be given as examples:

Case I. Mr. T., a well-to-do farmer, owning his own farm. Breakfast: Hominy, biscuits, butter, Molasses, and coffee; same the year round.

Dinner: Salt pork with vegetables; usually cabbage or turnips in winter, sometimes peas or beans; sweet potatoes from August to January; Irish potatoes, biscuits and cornbread.

Supper: What remained from dinner with cornbread; drank about a quart of buttermilk a day; seldom ate eggs, and had a chicken about once a week; had fresh pork occasionally in the winter

at hog-killing time. The family of seven, with five children, purchased monthly: 75 to 100 pounds of flour, 1½ bushels of cornmeal, sugar, and coffee.

Case II. Mrs. H., wife of well-to-do public accountant. Breakfast: Hominy with butter; hot bread and tea; during certain times of the year she ate an egg several times a week.

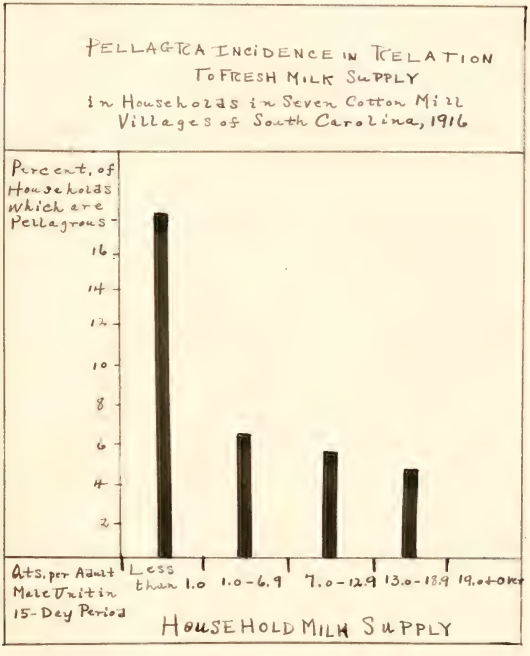
Dinner: Sweet potatoes or macaroni; occasionally ate a very little roast of beef; several biscuits; vegetables during summer, but few in winter.

Supper: Bread and grits, tea and sometimes cocoa. Drank very little milk, ate almost no meat, but was a hearty trencherton. Says she could have anything she wanted, but simply did not care for meat, eggs or milk.

From an examination of the above diets it is seen there is a deficiency in what are now known as the "protective foods", that is, meat, milk, eggs, and the leafy vegetables. The work of McCollum (38, 42) and others has shown definitely that no combination of foods is adequate for the optimum nutrition and well-being of an animal unless it has a fair share of the protective foods, especially milk, meat, and the leafy vegetables.

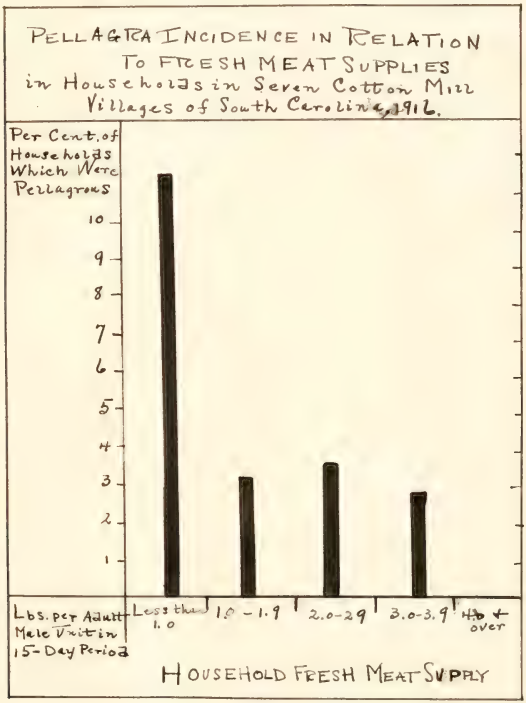
In a recent report concerning the relationship of diet to pellagra incidence, Goldberger and Wheeler (41) have brought forward some very interesting data in regard to the amount of milk and meat in the dietary of pellagrins. The results are shown graphically in the following charts taken from their report.

It is seen that the incidence of pellagra declined markedly as the milk supply of the households investigated increased, and that among households having a supply of one quart per adult male unit for the 15-day



period, the incidence was three times as great as in households which had larger supplies of milk. The data of Goldberger and Wheeler show too that the presence of a large milk supply in a household was not an indication of a better economic status and therefore of an ability to buy other possibly protective articles of diet, for non-pellagrous households with lowest incomes had an even larger average milk supply than did those with highest incomes. Further evidence also that pellagra was rel-

[illegible] households having a liberal supply of fresh milk was the incidence recorded for the ownership of milk cows. It was found that the incidence of the disease among households having



milk from such a source was less than 3 per cent. as against nearly 10 per cent. in families without a supply from such a source. Some of the older writers on pellagra had noticed that occupation had a relation to pellagra incidence, that is, that shepherds are almost all pellagrous in certain endemic areas in France, while [illegible] are rarely seen so, for the same reason himself in large

part with the milk from his cows.

The incidence of pellagra in relation to varying supplies of fresh meat is shown in the above diagram. It will be noted that pellagra declined in almost as marked a manner as in the case of milk; the incidence among households having a fresh-meat supply of less than one pound per adult male unit per 15-day period (approximately 30 grams per day) was more than three times as great as in households with a larger supply. It was also found that there was no close relation between the fresh-meat supply and the economic status.

In their study of diet in relation to the incidence of pellagra, Goldberger and Wheeler[41], in one of their recent reports, have come to some very definite conclusions. Comparisons of diets of non-pellagrous with those of pellagrous households revealed that the non-pellagrous enjoyed a more restricted supply of the foods of the "animal protein" group, such as lean meat, milk, butter, cheese, and eggs. Increasing supplies of milk or of fresh meat were found associated one independently of the other, with a decreasing pellagra incidence, but no correlation was found between varying supplies of other main meals, such as flour, or the common dried legumes and such incidence. It was also found that so far as fuel or calorific supply of foods is concerned that there was no great difference between pellagrous and non-pellagrous households, and the conclusion must be reached that there is some other factor in the character of the food supply which must be taken into consideration. So far as the question of protein is concerned it was noted that this

was somewhat less than in that of non-pellagrous families of comparable economic status, but even after allowing for waste the indicated somewhat liberal allowance considered by Chittenden as ample for physiologic needs, so that a deficiency in total protein would seem not to be an essential factor in relation to the incidence of the disease. The protein supply of the pellagrous households tended to include, on the one hand, a somewhat smaller proportion derived from animal foods and on the other a somewhat larger proportion from cereals and the common mature beans and peas, suggesting that the protein mixture, at least so far as amino-acids is concerned, in the diets of the non-pellagrous households is more likely to be physiologically adequate than that in the diet of the pellagrous groups.

It is interesting to note that the proportion of calories derived from carbohydrate and fat combined was essentially identical in the diet of the pellagrins and non-pellagrins, so that the production of pellagra would seem not to be dependent on the excessive consumption of these foodstuffs. However, the diets of the pellagrous households have a smaller average supply of the recognized "vitamines", in which the "protective foods" are rich, the disparity in supply being particularly marked with respect to the "fat soluble A" factor. The mineral content of the food is also usually deficient in case of the pellagrous households.

The data collected by Goldberger and Wheeler has led them to conclude that the pellagra-producing dietary fault is the result of one or a combination of two or more of the following factors: (1) a physiologically defective protein or amino-acid supply;

(2) a deficit or inadequate mineral supply; (3) a deficiency in an as yet unknown dietary essential (vitamine?); (4) The domestic hen's sense of supply, both of potential energy and of protein in its diet of foregoing scholas may act as contributory factors."

McCollum, Simmonds, and Parsons,[43] employing what they term the biological method of analysis have attempted to determine the exact nature of the deficiencies as are common among the people who subsist on foregoing. This consists in feeding a foodstuff which is faulty in one or more respects to a group of animals, and in another group the same food supplemented with one or more food additions, such as pure protein, one or more mineral salts, or one or more of the still unidentified dietary factors. These workers assume that the essential constituents of an adequate diet are protein of suitable quality and quantity, an adequate supply of certain inorganic salts or elements in suitable combinations, an adequate energy supply in the form of protein, carbohydrate, and fat, and the chemically unidentified dietary essentials "fat-soluble A" and "water-soluble B". The lack of the former causes the development of an eye disease described as xerophthalmia, while they claim that "water-soluble B is the substance which protects against the development of beriberi. It must be mentioned that others, notably Chick, Hume,[46] and Skelton (1918),[50] Drummond (1919) claim to have demonstrated the occurrence of a third essential factor which is designated "water-soluble C". This substance prevents the development of scurvy.

McCollum, Simmonds, and Parsons have

shown that there is a great difference between the vegetable foods which serve as storage organs, namely, roots, tubers, seeds, or their products, and the functionally active leaf with meta-protein. They were able to prepare fairly satisfactory diets with these two types of foods together, that is, the leaves and seeds, but broke down the group of vegetable foods which are functionally storage organs. Later on however, we do constitutes as to correct the dietary deficiencies of the storage organs, especially in respect to the inorganic elements or the fat-soluble A, and to some extent the proteins. Storage organs need supplementing in respect to calcium, sodium, and chlorine, as well as fat-soluble A.

In regard to the distribution of fat-soluble A in animal tissues, it was found especially abundant in the body fats of ruminants because they take larger quantities in their food. Butter, milk, and cheese are rich in this essential dietary principle, but muscle tissue is poor in it. Muscle tissue did not supplement as well the storage organs of plants as well as the body fats or glandular organs, because of the inadequacy in fat-soluble A. As already mentioned the "protective foods" include milk, eggs, and the leafy vegetables, and when used to sufficient extent will correct the faults of the remainder of the food if it is poor in the essential elements or substances. Milk is more efficient in this respect than the leafy vegetables; in fact, milk is a perfect food so far as its chemical constitution is concerned, and for this reason should form a fair portion of an adequate diet, although its place may be more or less substituted by certain of the other protective foods. Milk is also high in its per cent. of calcium, which is such an important inorganic constituent in the diet of growing

animals.

McCollum, Simmonds, and Parsons,[43] do not consider the minimum protein content as designated by Chittenden to be the amount which will lead to optimum well-being, activity, and nutrition, especially if continued over a considerable portion of the span of life of an animal. They conducted a series of experiments on rats to determine this point, and found that although the body weight was maintained for several months, or 8.4 per cent. the average span of life, the animals finally began to show signs of inadequate supply of protein in their diet. They lacked vitality, and soon began to show signs of senescence. These authors do not consider that experiments of only a few months, as carried out by Chittenden,[47] Goldberger,[39] and others, to test the effect of a restricted diet on man, should be given too much weight. Such experiments do not cover a sufficient per cent. of the span of life of a man. Some doubt is therefore cast upon such experiments, at least so far as producing the undoubted symptoms of pellagra in animals or man by such diets as these experimenters employed, although admittedly inadequate in many respects. McNeal has denied that Goldberger produced the disease in the prisoners which he used.

An inspection of the diets described by Goldberger as common in those institutions where pellagra is a common disease, and the winter diets of people in those districts where there is a high incidence of pellagra shows that these are composed largely of seeds and seed products, and that the amounts of leafy vegetables, milk, eggs, and meat, are very limited, or entirely absent for varying periods. McCollum[42] and Simmonds have pointed out that in the experimental diet with which Goldberger claims to have produced incipient pellagra in man, about

ninety-six per cent. of the total solids of the food supply was derived from seed products; they about four per cent. They point out that such a small amount of the leafy vegetables do not suffice to make good the dietary sufficiencies of the seed products in such a diet, so poor in the "protective foods". These authors point out further that the diets of those people who become pellagrins are deficient in three respects,- low in protein, the proteins being of poor biological value; an insufficient amount of fat-soluble A, and of certain mineral elements, notably Calcium, Chlorine, and Sodium; the Sodium Chloride is supplied as such in the form of table salt, but the element Calcium is still taken in insufficient amounts. They recommend the addition of Calcium Carbonate as a regular practice to such foods as are common among pellagrins so that the deficiency in this element may be made good.

Owing to the fact that there seems good evidence that there sometimes occur cases of pellagra in persons whose diet included a certain amount of the "protective foods", as well as the evidence brought out by these experimental work with rats, McCollum, Simmonds, and Parsons,[43] have concluded that although diet is the fundamental factor in the production of pellagra, it is not the only factor. They believe there must be also a bacteriological factor, for their rats fed on the restricted diet (wheat flour, peas, and cotton seed oil) did not develop the gastro-intestinal symptoms common in the disease in men, and which Chittenden and Underhill produced in dogs. They think that the sloughing of the mucous membranes and the presence of ulcers in

the isolation affords conclusive evidence of this secondary infectious agent. Goldberger has criticized these views, however, believing that the rat is an unsuitable animal for the production of pellagra as it has proven both for scurvy. The observations of McCollum[42] and his coworkers, however, have led them to believe that whether pellagra develops in man or animal restricted as to diet, is a matter of chance infection or relative immunity. It may be possible, and seems reasonable, that poor nutrition predisposes to infection, and that there is an infectious agent involved in the production of pellagra.

Prevention of the Disease:

After a discussion of the etiological factors involved in the production of pellagra, it is almost superfluous to say much of the steps which should be taken to prevent the occurrence of the disease. Education of the public as to the value of adequate diets, and what such diets are, is of the utmost importance, especially in those districts where the disease is endemic. That pellagra is primarily a disease of poverty no one can deny. Therefore any improvement in the general economic status of a community will tend to reduce the prevalence of the disease. Unfortunately, radical changes along such lines are hardly to be looked for in certain sections of the country where natural resources are poor to begin with. The best way to eradicate the disease in such districts is by active public health education. It is clear that the most important food for

recommended for consumption in pellagrous districts is milk, because of its cheapness compared with the same protective value in foods from other sources, and its three fold corrective character. Meat replaces the type of food found in pellagrous families only with respect to the protein factor; eggs are not so good as milk because their calcium content is not so high. The legume seeds, of high protein content, are, however, of little value for the improving the diets which predispose to the disease, because of the poor quality of their proteins.

Meat and eggs are now expensive than milk as protective foods against a faulty diet. Cow ownership is perfectly possible for many of even the poorest in the South, and education should be conducted to encourage it, as well as the consumption of a liberal supply of cheese, butter, fresh green vegetables, and fruit. There is no question that such prophylactic measures should greatly reduce the incidence of and the ravages of this terrible disease.

In addition, if bad sanitary conditions increase the incidence of the disease, improvement along these lines should be carried out. Cleanliness leads to personal as well as civic respect, and whatever raises the ideals of a community tends to bring about conditions for the betterment of public health in general.

Addendum.

Metabolism in Pellagra. In a recent article Sullivan, Stanton and Dawson[44], at the Pellagra Hospital at Spartanburg, S.C. have made some interesting observations on the metabolism in pellagra by a study of the urine. Commini appears to have been the first to have made a comparative study of metabolism in pellagra. He states that the diet of the Italian pellagrins is lacking in sodium and calcium. His work also included a study of the composition of the diet, the urine, and the feces of pellagrins subsisting on mixed diets and on diets composed largely of corn. Balances were obtained for nitrogen, fat and ash in comparison with those of normal individuals on similar diets. Commini found an increase in the excretion of chlorine associated as sodium chloride. Others have also found a decided negative mineral balance in active pellagra. Myers and Fine have found that the ability of individuals suffering from pellagra to utilize the various foodstuffs was but slightly if at all less than the normal. Hunter, Goins, and Lewis conclude that a diet providing 2500 calories and containing 15 grams of nitrogen (of which 11 grams are in the form of animal protein) is not only likely to promote the recovery of a pellagrin from an acute attack, but is adequate to meet all the requirements for maintenance and repair of his characteristics. In the study of the urine in pellagra at the U.S. Pellagra Hospital mentioned above, Sullivan, Stanton, and Dawson come to the following conclusions:

1. The mineral metabolism appeared to abnormal

efficiency in the active fulminous stage as witnessed by the low P_2O_5 excretion despite the fact that the diet taken at the time was a generous one with abundance of milk.

2. Indications were present of a heightened putrefactive process in the intestines as there was a high degree of indicanuria in the severe cases, although this is not always found.

3. The presence of casts and albumin gave evidence of more or less kidney change in 50% of the cases.

4. There was low excretion of total nitrogen and the urinary urinary coefficients.

5. The urea ratio, in general, was low and in certain cases with fair total nitrogen the urea ratio was lower than should be expected, a finding which suggests liver insufficiency.

6. There was a heightened ratio for ammonia nitrogen and undetermined nitrogen.

7. The metabolic work during the active stage of the disease was low as further shown by the low excretion of uric acid and creatinin.

8. The creatinin coefficient was much below normal.

9. The utilization of protein was found to be subnormal even after several weeks of a uremic diet.

10. Visit at least a month on the curative diet, the urinary ingredients rose to approximately normal amounts, the urea ratio rose to normal and the ammonia ratio fell to normal.

11. The abnormality in the urinary findings was greater for the systemic type than for the dermal type of the disease.

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